Microwave Assisted Solvent Free Synthesis of 2,7-(Substituted Phenyl)- 3-Phenyl-5,7,7A-Trihydro-2H-Thiazolo [4,5-D] [1,3] Thiazin-5-Amine Derivatives

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Abstract

Synthesis of Novel 2,7-(substituted phenyl)- -3-phenyl-5,7,7a-trihydro-2H-thiazolo [4,5-d] [1,3] thiazin-5-amine(Va-Vh) by condensation of 2-(substituted phenyl)-3-phenyl thiazolidin-4-one (IVa-IVh) with excess of aromatic aldehyde and thiourea dissolved in polar solvent. In vitro assay of newly synthesized compound were carried out to test antifungal activity by disc diffusion method against Fusarium oxysporum and Rhizoctonia solani. All synthesized compounds were characterized by UV.IR, ^{1}HNMR, ^{13}C NMR, spectral and elemental analysis.

Keywords- Thiazolidione, Thiazolo-Thiazine, Antifungal Activity

Introduction-:

Chemistry nowadays is at fore front of the development of clean production processes and products. Chemistry is no doubt determinant to understand and protect our environment, as the world's future is strongly dependant on the chemical processes adopted. Chemistry plays an integral part of our lives. Sustainability, eco-friendly and green chemistry are new principles that are guiding the development of next generation of products and processes[1,2]. "Green chemistry is considered an essential piece of a comprehensive program to protect human health and the environment." In its essence green chemistry[3-8] is a science based non-regulatory and economically driven approach to achieving the goals of environmental protection and sustainable development. Thiazoles are a familiar group of heterocyclic compounds possessing wide variety of biological activities, and their usefulness as medicines are well established. Thiazole nucleus is also an integral part of all the available penicillin's, which have revolutionized the therapy of bacterial diseases[9] . Thiazoles have attracted continuing interest because of their varied biologicalactivities[10] , which have found applications in the treatment of allergies[11], hypertension[12], inflammation[13], schizophrenia[14]microbial infections[15-16], HIV infections[17], hypnotics [18]and for the treatment of pain[19] . They have been also used asfibrinogen receptor antagonists with antithrombotic activity [20]and as new inhibitors of bacterial DNA gyrase B [21]. Aldo Andreani reported the synthesis and antitubercular activity of imidazo(2,1-b) thiazoles, Raghav Mishra, Synthesized and studied antimicrobial evaluation of some novel thiazole –pyrazoline derivatives. This has been prompted us to synthesize fused thiazo-thiazine derivatives.

Material and methods-: All chemicals used were of analytical grade. All the synthesized compounds have been characterized on the basis of chemical properties, elemental and spectral analysis. The melting points were measured in a open glass capillary and are uncorrected **.**IR spectra in KBr were recorded on instrument Perkin Elmer - Spectrum RX-IFTIR. ^{1}H-NMR spectra were recorded on FT NMR Spectrometer model Advance-II (Bruker) Its ^{1}H frequency is 400 MHz. ^{13}C the frequency is 100 MHz. ($CDCl_3$ and DMSO-d_6) using TMS as an internal standard All reactions were monitored by TLC using silica gel 60-f-254plates. All reactions were carried out in scientific microwave oven (Scientific microwave system model RG31lL1,700w, 2450MHz).satisfactory C,H,N analysis were carried out for most of the compounds on Thermo Scientific (FLASH 2000) CHN Elemental Analyzer at RSIC, Punjab university, Chandigarh

Synthesis Of 2,7-(Substituted Phenyl)- -3-Phenyl-5,7,7a-Trihydro-2h-Thiazolo [4,5-D] [1,3] Thiazin-5-Amine(Va-h)

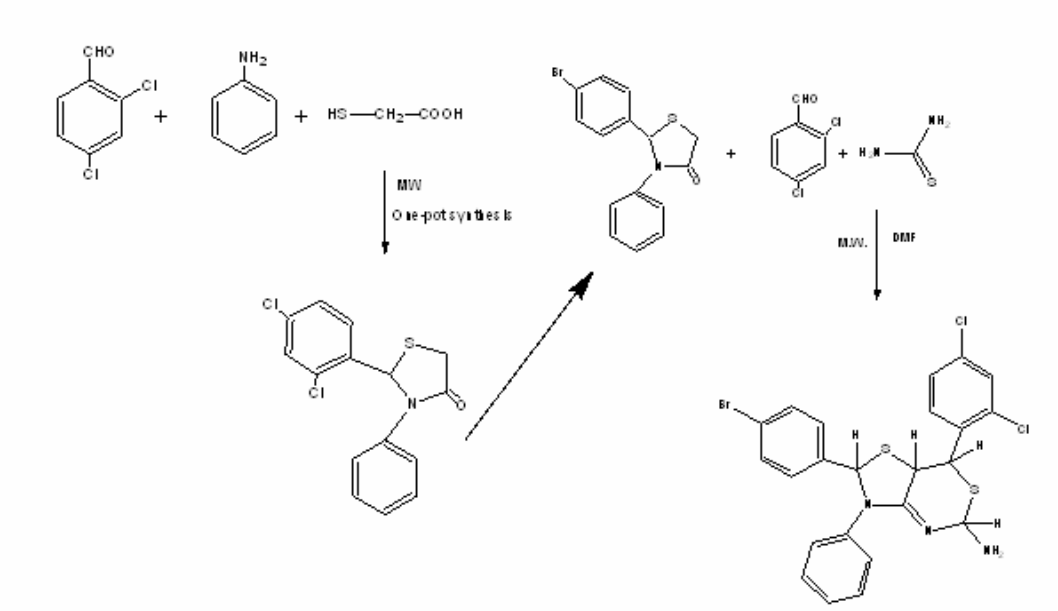
The reaction is completed in following two steps.

1)**Synthesis of 2-(substituted phenyl)-3-phenylthiazolidin-4-one(IVa-IVh)**-:A neat rection technology for one pot synthesis of the starting material 2-(substituted phenyl)-3-phenylthiazolidin)-4-one by condensation of aromatic aldehyde(0.01M), aniline(0.01M), and thioglycolic acid(0.01M). carried out under scientific microwave oven. The irradiation time is 1-1.5 min. The reaction mixture was cooled at room temperature and poured in ice-cold water. The product thus separated out was filtered and crystallized from ethanol to get fine crystals of 2-(substituted phenyl)-3-phenylthiazolidin-4-one . (IVa-IVh).

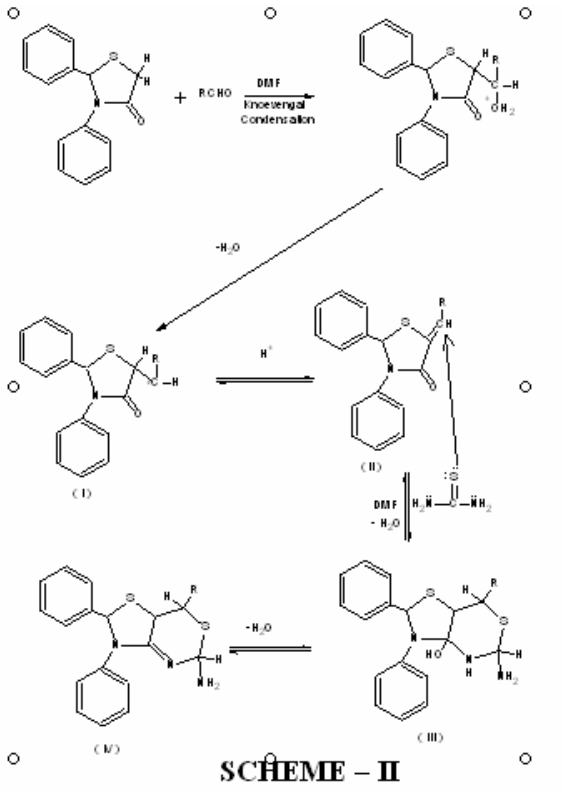
II) Synthesis of 2,7-(substituted phenyl)-3-phenyl-5,7,7a-trihydro-2H-thiazolo [4,5-d] [1,3] thiazin-5 –amine(Va-Vh)-: The synthesis of Novel 2,7-(substituted phenyl)- -3-phenyl-5,7,7a-trihydro-2H-thiazolo [4,5-d] [1,3] thiazin-5-amine(Va-Vh) by condensation of 2-(substituted phenyl)-3-phenyl thiazolidin-4-one.(0.01M) (IVa-IVh) with excess of aromatic aldehyde and thiourea dissolved in polar solvent under microwave mode (1.5 min) followed by filtration, washing with water and recrystallize from ethanol to get the product

Mechanism

Thiazolidione are the potential synthons in the synthesis of heterocyclic compounds. It is noteworthy that the reactivity of thiazolidione is due to inductive effect of carbonyl group. Thiourea is a weak base ,the reason is that the lone pair of electrons on nitrogen are removed in the formation of ∏- molecular orbital. In this mechanism the first step concern with Knoevengel condensation of thiozalidione and aldehyde through carbonium ion intermediate in situ results in the formation of α-β unsaturated ketone and second step involve nucleophilic addition of thiourea followed by cyclodehydration to lead target molecule.



SCHEME – I Experimental scheme for the synthesis of2,7-(substituted phenyl)-3-phenyl-5,7,7a-trihydro-2H-thiazolo [4,5-d] [1,3] thiazin-5 –amine(Va-Vh) (IVa-h)



SCHEME – II

Table I: Physical data of of2,7-(substituted phenyl)-3-phenyl-5,7,7a-trihydro -2H-thiazolo [4,5-d] [1,3] thiazin-5 –amine(Va-Vh

Compound (Va-Vh)	R	R_1	R_2	*Molecular Formula*	*Melting Point*
a	$-C_6H_5$	$-C_6H_4Cl$	$C_6H_3Cl_2$	$C_{23}H_{18}Cl_3N_3S_2$	265^0C
b	$-C_6H_5$	$-C_6H_4OH$	C_6H_4Br	$C_{23}H_{20}BrN_3OS_2$	270^0C
c	$-C_6H_5$	$-C_6H_4Br$	$C_6H_3Cl_2$	$C_{23}H_{18}BrCl_2N_3S_2$	284^0C
d	$-C_6H_5$	$-C_6H_4$-OCH_3	C_6H_4Br	$C_{24}H_{22}BrN_3OS_2$	264^0C
e	$-C_6H_5$	$-C_6H_4Cl$	$-C_6H_5$	$C_{23}H_{20}ClN_3S_2$	274^0C
f	$-C_6H_5$	$-C_6H_5$	$-C_6H_3Cl_2$	$C_{23}H_{19}Cl_2N_3S_2$	283^0C
g	$-C_6H_5$	$-C_6H_4Br$	$-C_6H_5$	$C_{23}H_{20}BrN_3S_2$	254^0C
h	-C6H5	$-C_6H_5$	$-C_6H_5$	$C_{23}H_{21}N_3S_2$	263^0C

Spectral data

1)2-(4-bromophenyl)- 7-(2,4-dichlorphenyl)3-phenyl-5,7,7a-trihydro-2H-thiazolo [4,5-d] [1,3] thiazin-5 –amine(V c)

M.wt:-551.35 gm, M.P:-284^0**C,** brownish crystalline solid **IR(cm-1):** 3303(-NH_2) ,3058[C-H st (aromatic)], 2900[C-Hst (aliphatic)], 1693(C=N), 1618 (N-H bend), 1597 [C=C], 1490 [C-N], 1100 [C-Cl(aryl halide)], 692[N-H wagging] ;^{1}**HNMR:**-400 MHz (CDCl3): 3.3[(s,1H,-CH(W-coupling)],3.5(d,2H,NH2) ,3.6[(S,1H, ,-CH(W-coupling)], 3.8(d,1H,-CH ,J^3-15.7Hz) ,3.9(d,1H,-CH ,J^3-15.7Hz)6.4-8.0(m,12H,Ar-H);^{13}CNMR-100 MHz. ($CDCl_3$ and DMSO-d_6) 63.48(C-N,62.79(-CH),32.71(CH)121.07(CNH2),127.97,170.36,130.97,131.35,126.47,137.17,147.7,125.46,128.22,121.37, 139.54,128.67,131.55,137.42,188.74(C=N) calculated %C= 50.10 %N=7.62 %S =11.63 % Br=14.49 % Cl=3.29 % H= 12.86 observed %C= 50.02 %N= 7.12 %S =11.06 % Br= 14.11 % Cl =2.45 % H=12.21

2) **2-(methoxyphenyl)-7-(4-bromophenyl)3-phenyl-5,7,7a-trihydro-2H-thiazolo [4,5-d] [1,3] thiazin-5 –amine(V d)**

M.wt:-511.04 gm, M.P:-264^0**C,** brownish crystalline solid **IR(cm-1):** 3400(-NH assym) ,3258 (NH sym),3058[C-H st (aromatic)], 2940[C-Hst (aliphatic)], 1723(C=N), 1600 (N-H bend), 1625 [C=C], 1444 [C-N], 1067 [C-Br(aryl halide)], 960[N-H wagging] ;^{1}**HNMR:**-400 MHz (CDCl3): 1.28(s,3H,OCH_3), 3.6[(s,1H,-CH(W-coupling)],3.37(Br,2H,NH2) ,3.7[(d,1H, ,-CH(W-coupling)], 4.2(d,1H,-CH ,J^3-7.2Hz) ,4.3(d,1H,-CH ,J^3-7.2Hz),7.0-7.7(m,12H,Ar-H);^{13}CNMR-100 MHz.($CDCl_3$and$DMSOd_6$)63.22(CN),61.29(OCH3),43.14(CH)113.86(CNH2),13.8(CH) ,130.18,128.62,131.99,159.16,138.74,119.23,128.75,123.34,138.83,131.46,131.65,123.52(Ar-CH),167.03(C=N) calculated %C= 56.25 %N=8.20 %S =12.51 % Br=15.59 % O=3.12 % H= 4.33 observed %C= 56.12 %N= 7.98 %S =12.01 % Br= 15.21 % O =2.94 % H=4.33

Antifungal Activity-: All the synthesized compounds were screened for their antifungal activity viz. *fusarium oxysporum, Rhizoctonia solani* by using disc diffusion method for their antifungal activity.The punch discs of 6.25 mm diameter of Whatman filter paper no. 1 were prepared and dispensed in the batches of 100 each in screw capped bottles. These were sterilized by dry heat at 140^0C for 60 minutes. The solutions of 1000 ppm and 100 ppm concentrations of test compounds were prepared in dimethyl formamide (DMF) solvent separately. The discs were soaked, assuming that each disc will contain approximately 0.01 ml of test solution

Table 2 - In vitro antifungal screening of above tested compounds

Sr.No.	Tested Compounds	Fungus (zone of inhibition in mm)			
		Fusarium oxysporum		*Rhizoctonia solani*	
		100 ppm	1000 ppm	100ppm	1000ppm
1	Va	6	7	-	12
2	Vb	15	17	14	18
3	**Vc**	**32**	**34**	**31**	**34**
4	Vd	26	28	18	20
5	Ve	20	21	16	18
6	Vf	11	12	9	11
7	Vg	17	18	21	26
8	Vh	9	13	8	10

The observations show that activity of compound Vc is maximum against both the fungi . Almost all the compounds were active against all the test pathogens. The compound 5c is the most dominant among all the test compounds. Their inhibitory impact on the bacterial growth is remarkable.

Conclusion

This was an attempt to synthesize biologically potential heterocyclic moiety in solvent free reaction condition that leads to considerable saving in the reaction time and energetically profiTable. The solvent free condition contributes to saving in cost, time and diminishes the waste disposal problem and environmental pollution this work may bring research fraternity towards sustainable development.

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